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TITLE: Targeted adenovirus vectors

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Detailed Description Text - DETX (22):

Following intravenous administration of the adenovirus vector, three distinct sequential steps are required for targeted expression of the therapeutic gene in specific cells: (1) attachment of the adenovirus vector to specific receptors on the surface of the target cell; (2) internalization of the virus; and (3) transfer of the gene to the nucleus where it can be expressed. Thus any attempt to modify the tropism of an adenovirus vector must retain its ability to perform these three functions efficiently. Furthermore, the modification of adenovirus tropism must be approached with knowledge of the biology of adenovirus infection (FIG. 1). It has recently been shown that the globular carboxy-terminal "knob" domain of the adenovirus fiber protein is the ligand for attachment to the adenovirus cellular receptor, the first step in infection. A trimeric fiber protein protrudes from each of the 12 vertices of the icosahedral viral particle where it is attached noncovalently to the penton base. The amino-terminal tail is separated from the knob domain by a long rod-like shaft comprising a 15-amino acid residue motif repeated 22 times in human adenovirus types 2 and 5. The knob is both necessary and sufficient for virion binding to host cells. Following attachment, the next step in adenovirus infection is internalization of the virion by receptor-mediated endocytosis. This process is mediated by the interaction of Arg-Gly-Asp (RGD) sequences in the penton base with secondary host cell receptors, integrins avb3 and avb5. Post-internalization, the virus is localized within the cellular vesicle system, initially in clathrin-coated vesicles and then in cell endosomes. Acidification of the endosomes allows the virions to escape and enter the cytosol. This step has been hypothesized to occur via a pH-induced alteration in the hydrophobicity of the adenoviral capsid proteins which allows their interaction with the cell vesicle membrane. The virion then localizes to the nuclear pore and its genome is translocated to the nucleus of the host

cell. This understanding of the adenovirus entry pathway is required to modify the tropism of adenoviral vectors to permit the targeting of specific cell types.